A Clinical Index to Define Risk of Asthma in Young Children with Recurrent Wheezing

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Because most cases of asthma begin during the first years of life, identification of young children at high risk of developing the disease is an important public health priority. We used data from the Tucson Children's Respiratory Study to develop two indices for the prediction of asthma. A stringent index included frequent wheezing during the first 3 yr of life and either one major risk factor (parental history of asthma or eczema) or two of three minor risk factors (eosinophilia, wheezing without colds, and allergic rhinitis). A loose index required any wheezing during the first 3 yr of life plus the same combination of risk factors described previously. Children with a positive loose index were 2.6 to 5.5 times more likely to have active asthma between ages 6 and 13 than children with a negative loose index. Risk of having subsequent asthma increased to 4.3 to 9.8 times when a stringent index was used. We found that 59% of children with a positive loose index and 76% of those with a positive stringent index had active asthma in at least one survey during the school years. Over 95% of children with a negative stringent index never had active asthma between ages 6 and 13. We conclude that the subsequent development of asthma can be predicted with reasonable accuracy using simple, clinically based parameters.

Recent longitudinal studies have suggested that, in a large proportion of all cases of asthma, asthmalike symptoms begin during the first years of life (1). Moreover, a long-term follow-up of children with different degrees of asthma severity enrolled in Melbourne, Australia, at the ages of 7 to 10 yr suggests that severity of asthma changes little with time (2). As a consequence, it is the children with the most severe asthma during the school years who become the most severe asthmatics during adult life and up to the age of 35. Children with mild infrequent asthma, on the other hand, have either mild symptoms in early adult life or their symptoms may remit indefinitely (2). Our own studies have also suggested that children who had wheezing lower respiratory tract illnesses during the first 3 yr of life and whose wheezing episodes persisted up to the age of 6 have significantly lower levels of lung function at age 6 compared with children whose wheezing symptoms started after the age of 3 (3). Taken as a whole, these data indicate that early initiation of asthma symptoms is associated with more significant functional deterioration and more persistence of symptoms into adult life (4–6).

The aforementioned considerations have suggested that identification of symptomatic infants and young children who will go on to develop asthma may be very important for the development of a strategy for early intervention aimed at changing the natural course of the disease (4). Unfortunately, wheezy infants who will go on to develop asthma coexist with a larger group of their peers who also wheeze in early life but whose symptoms are transient and usually subside during the preschool or early school years (7). Distinguishing these two asthmalike phenotypes during infancy and early childhood simply on the basis of their clinical presentation is problematic. There are still no reliable genetic markers available and the use of any single biochemical marker is still controversial (1). It is possible, however, that by use of both clinical data and simple, easily obtainable laboratory information, a combination of these parameters may be used to identify children at high risk of developing persistent symptoms in a clinical setting.

In the present study, we used the longitudinal data available in the Tucson Children's Respiratory Study to describe predictive indices for asthma during the school years among children having wheezing episodes during the first 3 yr of life.

METHODS

The Tucson Children's Respiratory Study is a large, longitudinal assessment of respiratory illnesses in children (8). Eligible participants were healthy infants born to parents who planned to use the pediatricians of a large health maintenance organization in Tucson. A total of 1,246 newborns and their families (78% of those eligible) were enrolled at birth between 1980 and 1984. Detailed information about enrollment has been published elsewhere (8).

At the time of enrollment, the parents completed a questionnaire about parental (either father or mother) history of a physician diagnosis of asthma ("parental MD asthma") and prenatal maternal smoking status. Parents of enrolled children were asked to complete questionnaires regarding their child's history of respiratory conditions and health at different ages during childhood: Yr 2 survey (mean [± SD] age, 1.6 ± 0.4 yr), Yr 3 survey (age, 2.9 ± 0.5 yr), Yr 6 survey (age, 6.3 ± 0.9 yr), Yr 8 survey (age, 8.6 ± 0.7 yr), Yr 11 survey (age, 10.9 ± 0.6 yr), Yr 13 survey (age, 13.5 ± 0.6 yr).

Asthma and Wheezing Data

At the Yr 2 and Yr 3 surveys, parents were asked whether the child's chest had ever sounded wheezy or whistling and how frequently the child had wheezed (scale: 1 to 5, from "very rarely" to "on most days"). We considered that a child was an "early wheezer" if his or her chest had ever sounded wheezy and an "early frequent wheezer" if the parents reported a value ≥ 3 in the scale. Parents were also asked if wheezing occurred only with colds or also apart from colds. We classified a child as having "wheezing apart from colds" if this symptom was reported in at least one of these two surveys.

At the Yr 6, Yr 8, Yr 11, and Yr 13 surveys parents were asked if the child had wheezed during the previous year and about the frequency of wheezing episodes. A child was considered to have developed "active asthma" if he or she had asthma diagnosed by a physician with at least one episode of asthma during the previous year or had more than three episodes of wheezing during the previous year regardless of a diagnosis of asthma (9).

Markers of Atopy

As part of the Yr 2 and Yr 3 surveys, parents were asked whether the child had hay fever or any other condition that made his or her nose stuffy, itchy, or runny apart from colds during the past year and whether a doctor had said that these symptoms were due to allergies. We classified children as having "MD allergic rhinitis" if this condition was present in at least one of these two surveys (10). In addition, children were considered to have "MD eczema" if a physician had di-

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TABLE 1

A CLINICAL INDEX TO DEFINE ASTHMA RISK*

Major Criteria	Minor Criteria
1. Parental MD asthma†	1. MD allergic rhinitis§
2. MD eczema‡	2. Wheezing apart from colds
	3. Eosinophilia (⩾ 4%)

* Loose index for the prediction of asthma: Early wheezer plus at least one of two major criteria or two of three minor criteria. Stringent index for the predication of asthma: Early frequent wheezer plus at least one of two major criteria or two of three minor criteria.

† History of a physician diagnosis of asthma.

‡ Physician diagnosis of atopic dermatitis as reported in questionnaires at ages 2 or 3.

§ Physician diagnosis of allergic rhinitis as reported in questionnaires at ages 2 or 3.

agnosed this condition during the previous year as reported either in the Yr 2 or Yr 3 surveys.

Blood specimens were obtained at (mean ± SD) age 10.9 ± 0.6 mo, and circulating eosinophils (as percentage of total white blood cells) were calculated. "Eosinophilia" was considered to be present if eosinophils were ⩾ 4% of the total white blood cells.

Asthma Predictive Indices

To classify children as potentially at risk for asthma at school age, we developed two indices. For the "stringent index for the prediction of asthma", children had to be defined as an early frequent wheezer during the first 3 yr of life and meet at least one of two major criteria (parental MD asthma or MD eczema in the child) or two of three minor criteria (MD allergic rhinitis, wheezing apart from colds, or eosinophilia). For the "loose index for the prediction of asthma" the child had to be defined as an early wheezer during the first 3 yr of life and meet one of two major criteria or two of three minor criteria (as previously described) (Table 1). The variables used to develop the indices were chosen because, in univariate analysis, there were significant predictors of the subsequent development of asthma. This particular combination of major and minor criteria was chosen because it provided the highest positive predictive value and the highest specificity with respect to subsequent asthma.

Statistical Analysis

We assessed sensitivity, specificity, positive predictive value, and negative predictive value for both asthma predictive indices with respect to active asthma at the Yr 6, Yr 8, Yr 11, and Yr 13 surveys. Sensitivity is defined as the probability that schoolchildren with active asthma had a positive asthma predictive index. Specificity is defined as the probability that schoolchildren without active asthma during the school years had a negative asthma predictive index. Positive predictive value is defined as the probability that an infant with a positive asthma predictive index had active asthma during the school years. Negative predictive value is defined as the probability that an infant with a negative asthma predictive index was not classified as having active asthma during the school years.

The chi-square test was used to compare proportions. The 95% confidence intervals (CI) for sensitivity, specificity, positive predictive value, and negative predictive value, were calculated using the binomial distribution (11). Statistical significance was defined by a two-sided alpha level of 0.05. This study was approved by the Human Subjects Committee at the University of Arizona, and informed consent was obtained from parents.

TABLE 2

PREVALENCE OF POSITIVE LOOSE AND STRINGENT INDEX FOR THE PREDICTION OF ASTHMA AMONG CHILDREN INCLUDED OR NOT INCLUDED IN THE STUDY AT DIFFERENT SURVEYS

	Positive Loose Index for the Prediction of Asthma			Positive Stringent Index for the Prediction of Asthma		
Survey	Included % (n)	Not Included % (n)	p Value	Included % (n)	Not Included % (n)	p Value
At Yr 6	23.4 (928)	27.6 (58)	0.46	6.3 (994)	6.9 (58)	0.84
At Yr 8	23.1 (780)	25.7 (206)	0.43	4.9 (790)	11.3 (212)	0.0007
At Yr 11	23.6 (867)	23.5 (119)	0.98	5.7 (881)	10.7 (121)	0.03
At Yr 13	22.0 (655)	26.9 (331)	0.09	5.0 (664)	8.9 (338)	0.02

TABLE 3

FREQUENCY OF DIFFERENT TRAITS USED TO DEVELOP THE ASTHMA PREDICTIVE INDICES BEFORE AGE 3, BY SEX

Traits	Males % (n)	Females % (n)	Total % (n)
Early wheezer	57.0* (526)	50.6 (551)	53.8 (1,077)
Early frequent wheezer	14.3† (526)	7.3 (551)	10.7 (1,077)
Major criteria			
Parental MD asthma	23.1 (541)	22.2 (553)	22.7 (1,094)
MD eczema	13.2 (523)	10.8 (548)	12.0 (1,071)
Minor criteria			
MD allergic rhinitis	18.3 (520)	15.6 (546)	16.9 (1,066)
Wheezing apart from colds	17.9‡ (526)	12.1 (553)	14.9 (1,079)
Eosinophilia ⩾ 4%	9.7 (454)	10.9 (458)	10.3 (912)

* $p = 0.04$, † $p = 0.0002$, ‡ $p = 0.008$ in comparison to females.

RESULTS

Of the 1,246 children who were enrolled, 79.1% and 80.4% had complete information for a combination of major/minor criteria that allowed us to determine their loose or stringent index for the prediction of asthma, respectively. Among children with a positive loose index for the prediction of asthma, there were no differences between the percentages included in or excluded from the analysis at each survey (Table 2). In contrast, a higher proportion of children with a positive stringent index for the prediction of asthma was not included at the Yr 8, Yr 10, and Yr 13 surveys when compared with those with a negative stringent index for the prediction of asthma (Table 2).

The frequency of the different parameters used to develop the asthma predictive indices is shown in Table 3. Males were more likely than females to be early wheezers and early frequent wheezers and also were more likely to have wheezing apart from colds (Table 3).

A total of 986 children had complete information for the variables used to determine loose index for the prediction of asthma. Of these 986 children, 233 (23.6%) had a positive index, with more males than females being positive (26.5% versus 20.8%, respectively, $p = 0.036$, odds ratio [OR] = 1.4, 95% CI = 1.0 to 1.8). Of the 1002 children who had complete information for the stringent index for the prediction of asthma, 63 (6.3%) had a positive index, with more males than females being positive (8.7% versus 4.0%, respectively, $p = 0.002$, OR = 2.3, 95% CI = 1.3 to 3.9).

TABLE 4

PREVALENCE (%) OF ACTIVE ASTHMA AT DIFFERENT SURVEYS AND ACTIVE ASTHMA IN AT LEAST ONE SURVEY, BY SEX

Active Asthma	Males % (n)	Females % (n)	OR (95% CI)	p Value
At yr 6	13.8 (492)	8.4 (522)	1.3 (1.1–1.7)	0.006
At yr 8	17.5 (401)	10.1 (424)	1.4 (1.1–1.8)	0.002
At yr 11	20.6 (461)	11.3 (486)	1.5 (1.2–1.8)	0.00009
At yr 13	19.3 (337)	15.8 (360)	1.1 (0.9–1.4)	0.2
In at least one survey	39.3 (356)	31.0 (356)	1.2 (1.0–1.4)	0.02

TABLE 5

SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE, AND NEGATIVE PREDICTIVE VALUE OF THE LOOSE INDEX FOR THE PREDICTION OF ASTHMA FOR ACTIVE ASTHMA AT YR 6, YR 8, YR 11, AND YR 13 SURVEYS

Active Asthma	OR* (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive p Value % (95% CI)	Negative p Value % (95% CI)
At Yr 6 (n = 921)	5.5 (3.5–8.4)	56.6 (53.3–59.9)	80.8 (78.3–83.3)	26.2 (23.4–29.0)	93.9 (92.4–95.4)
At Yr 8 (n = 776)	4.4 (2.8–6.8)	50.5 (47.0–54.0)	81.1 (78.3–83.9)	29.4 (26.2–32.6)	91.3 (89.3–93.3)
At Yr 11 (n = 861)	2.6 (1.8–3.8)	40.1 (36.8–43.4)	79.6 (76.9–82.3)	27.1 (24.1–30.1)	87.5 (85.3–89.7)
At Yr 13 (n = 644)	3.0 (1.9–4.6)	39.3 (35.5–43.1)	82.1 (79.1–85.1)	31.7 (28.1–35.3)	86.5 (83.9–89.1)
In at least one survey (n = 651)	3.9 (2.7–5.7)	41.6 (37.8–45.4)	84.7 (81.9–87.5)	59.1 (55.3–62.9)	73.2 (69.8–76.6)

* $p < 0.00001$: between positive versus negative loose index for prediction of asthma for active asthma at each survey.

Table 4 shows the prevalence of active asthma at different surveys during the school years and in at least one survey. Prevalence of active asthma and active asthma in at least one survey were significantly higher in males than in females at all ages up to Yr 11 but not at the Yr 13 survey.

Children with a positive loose index for the prediction of asthma were 2.6 to 5.5 times more likely to have active asthma some time during the school years than children with a negative loose index for the prediction of asthma (Table 5). Risk of having subsequent active asthma increased to 4.3 to 9.8 times when the stringent index was used (Table 6).

Table 5 also shows sensitivity, specificity, positive predictive value, and negative predictive value of the loose index for active asthma at different school age surveys. As expected, sensitivity decreased with age, whereas specificity was consistently around 80%, and attained 84.7% for asthma in at least one survey. Positive predictive value was quite constant, and 59.1% of subjects with a positive predictive index had active asthma in at least one survey. Negative predictive value was consistently high, ranging from 86.5% at Yr 13 to 93.9% at Yr 6 survey. Using the stringent index sensitivity was quite low in all surveys (Table 6). However, specificity increased to over 96% consistently and positive predictive value increased to 76.6% for active asthma in at least one survey. The negative predictive value remained consistently high (Table 6).

DISCUSSION

In this longitudinal study, we used six parameters that can easily be obtained in any clinical practice (namely, frequency of wheezing, history of eczema, parental history of asthma, eosinophilia, allergic rhinitis, and wheezing without colds), to assess the risk of subsequent development of asthma in infants and young children. As expected, a stringent index that required subjects to have wheezed more frequently in early life plus other risk factors for asthma had an acceptable positive predictive value and a very high specificity, but its sensitivity was quite low. Conversely, a more loose index, which only required infrequent wheezing episodes plus the same combination of other risk factors included in the stringent index had a much higher sensitivity but lower specificity and positive predictive values. The negative predictive value at all ages was very high for both indices, suggesting that the great majority of children who did not develop asthma during the school years had a negative predicted index during the first years of life.

The main objective of this study was to determine the accuracy with which, using simple clinical parameters, the subsequent development of asthma could be predicted in a general population sample. This exercise may have very important implications for any strategy aimed at early intervention in subjects at high risk of developing asthma. It has been postulated that early intervention with anti-inflammatory drugs could change the natural course of the disease (12). Although there is some indirect evidence supporting this hypothesis (13, 14), it is by no means conclusive. Nevertheless, it would be reasonable for clinicians treating infants and young children with recurrent wheezing to be more aggressive with those subjects expected to be less likely to undergo remission from their symptoms. As with any study of this type, our results suggest that if the criteria to select at-risk individuals are very stringent, the index is able to predict with a reasonable degree of accuracy (over 75%) which children who are wheezing in early life will have significant asthma symptoms at least once during the school years. However, many children who will go on to develop significant asthmalike symptoms later in life have only mild wheezing episodes in early life, and therefore, the sensitivity of the stringent index is quite low. Conversely, if the criteria used to include children in the at-risk group are made more loose, the proportion of children who will

TABLE 6

SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE, AND NEGATIVE PREDICTIVE VALUE OF THE STRINGENT INDEX FOR THE PREDICTION OF ASTHMA FOR ACTIVE ASTHMA AT YR 6, YR 8, YR 11, AND YR 13 SURVEYS

Active Asthma	OR* (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive p Value % (95% CI)	Negative p Value % (95% CI)
At Yr 6 (n = 937)	9.8 (5.6–17.2)	27.5 (24.6–30.4)	96.3 (95.1–97.5)	47.5 (44.3–50.7)	91.6 (89.8–93.4)
At Yr 8 (n = 775)	5.8 (2.9–11.2)	16.3 (13.7–18.9)	96.7 (95.4–98.0)	43.6 (40.1–47.1)	88.2 (85.9–90.5)
At Yr 11 (n = 875)	4.3 (2.4–7.8)	15.0 (12.6–17.4)	96.1 (94.8–97.4)	42.0 (38.7–45.3)	85.6 (83.3–87.9)
At Yr 13 (n = 653)	5.7 (2.8–11.6)	14.8 (12.1–17.5)	97.0 (95.7–98.3)	51.5 (47.7–55.3)	84.2 (81.4–87.0)
In at least one survey (n = 659)	7.1 (3.5–14.1)	15.7 (12.9–18.5)	97.4 (96.2–98.6)	76.6 (73.4–79.8)	68.3 (64.7–71.9)

* $p < 0.00001$: between positive versus negative stringent index for the prediction of asthma for active asthma at each survey.

have asthma and who have a positive index (sensitivity) increases significantly, but the positive predictive value decreases. This means that a high proportion of children who will not go on to develop asthma will have a positive index. In the final analysis, a decision about which of the two indices should be applied will depend on the efficacy and potential side effects of any preventive measures to be recommended for at-risk subjects. A potential treatment with high efficacy but with significant potential side effects should probably only be used in children with a very high risk of disease, that is, those with a positive stringent index. This would avoid treating a large number of children who will not go on to develop asthma with a regimen that may be prone to generate unnecessary side effects in such a population. Conversely, for a treatment regimen of low efficacy but also with little or no side effects a loose index for the prediction of asthma would be reasonable.

It is worth noting that our stringent index had a rather low sensitivity (14.8 to 27.5%). Sensitivity increased markedly when using a looser index (39.3 to 56.6%). This suggests that, for many cases of childhood asthma, symptoms are rather mild in early life and become more severe with age. This is in agreement with our own previous reports suggesting that children who wheeze in early life and are still wheezing at age 6 have apparent deficits in lung function at age 6 compared with the levels of lung function they started with during the first months of life (3). This would suggest, that from a clinical point of view, the loose index for the prediction of asthma would be able to pick up most of the children who will have asthma in early life and whose symptoms will persist beyond that age. Interestingly, we found that, for children whose asthmalike symptoms started after the age of 3, no significant loss in lung function was observed up to the age of 11 yr, even among those whose symptoms persisted up to that age (15). It is thus likely that the loose index for the prediction of asthma will be able to detect most children at risk for developing progressive disease, that is, asthma of early onset. Still, as explained previously, over 40% of all children who have a positive loose index will never have active asthma during the school years. This compares with less than 25% of children who have a positive stringent index.

There are some potential sources of bias that need to be considered when interpreting our results. Researchers involved in this study had no participation in the day-to-day clinical management of symptomatic children. What role treatment may have in the associations under study is difficult to assess. However, it is important to point out here that until very late during the follow-up, inhaled steroids were seldom, if ever, used in the treatment of asthma in these children (data not shown). Any effects of treatment would tend to decrease the predictive power of the calculated indices. It is also possible that parents of children who had symptoms in early life may be more prone to report milder symptoms in their children later in life than parents of children with no symptoms in early life. However, we have observed a strong correlation between reported symptoms and objective indices of asthma activity at different ages (16). It is thus unlikely that this source of bias may have significantly influenced our results.

We know of only one other study that has attempted the same type of longitudinal assessment reported herein. Clough and coworkers (17) recently reported the 12-mo outcome of a smaller group of children (n = 109) enrolled at a mean age of 11 mo. All enrolled children had at least one atopic parent. Using personal and family history of atopy, and immune parameters measured in blood, they reported sensitivities that were much higher than those observed in our study, although their specificity, positive predictive values, and negative predictive values were similar to ours. However, both the design of the study, length of the follow-up, and inclusion criteria were very different in Clough and coworkers' study (17) and in ours, so results may not be directly comparable. In addition, we chose simple, easily measurable parameters that could be obtained in any clinical setting. It is possible that inclusion of more complex immune parameters in our indices may increase their predictive capacity, but we believe that this would hamper their general clinical application.

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Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma

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Background: Few studies have characterized the atopic profile of toddler-aged children with recurrent wheezing at high risk of the development of persistent asthma.

Objective: We sought to determine the atopic profile of toddler-aged children with frequent wheeze at high risk for the development of persistent asthma who either had a parental history of asthma, a personal history of atopic dermatitis, or both.

Methods: Participants enrolled in the Prevention of Early Asthma in Kids study (n = 285) on the basis of a modified Asthma Predictive Index were characterized on the basis of allergy and asthma questionnaire responses and allergy skin puncture test results.

Results: The majority of the children (60.7%, n = 148) were sensitized to either food or aeroallergens. Male children were significantly more likely to be sensitized to aeroallergens ($P = .03$) and to have a blood eosinophil level of 4% or greater ($P = .03$) and a total serum IgE level of greater than 100 IU/mL ($P = .0004$). Additionally, eosinophilia and total serum IgE level had the strongest correlation with aeroallergen sensitization.

Conclusion: The high prevalence of aeroallergen sensitization in this high-risk cohort suggests that aeroallergens might have an important role in the early development of asthma. As such, the Prevention of Early Asthma in Kids cohort appears to be an appropriate cohort in which to test whether early intervention with an inhaled corticosteroid can significantly attenuate, or perhaps even prevent, the allergic march from the initial stages of allergic sensitization to the subsequent development of asthma in toddlers with episodic wheezing. (J Allergy Clin Immunol 2004;114:1282-7.)

Key words: *Allergens, aeroallergen and food sensitization, asthma predictive index, atopy, clinical trials, early childhood asthma, fluticasone, glucocorticoids, intermittent wheezing, prevention of asthma, research network, skin prick test*

Asthma remains a significant public health problem in the United States in the pediatric age group.[1] Not only is the prevalence of the disease increasing, especially during the early school years, but studies of the natural history of the disease have demonstrated that in most cases of persistent asthma the initial asthma-like symptoms occur during the first several years of life.[2] Thus it is important to understand the clinical features of very young children who might be at risk for the development of persistent asthma. In addition, few studies exist that characterize the atopic profile of toddler-aged children with frequent recurrent wheezing and the events that follow in terms of the so-called allergic march. We describe the atopic profile of a large number of high-risk toddler-aged children identified by using a modified Asthma Predictive Index (mAPI)[3] who were enrolled in a long-term secondary asthma prevention study. Our hypothesis is that the majority of toddler-aged children who are at high risk for the development of asthma will be sensitized to aeroallergens and that this sensitization might be modified by sex and ethnicity.

METHODS

Subjects

Children 2 and 3 years of age with frequent intermittent wheezing at high risk of persistent asthma but without persistent symptoms were identified by meeting the criteria for a positive mAPI result and enrolled in the Prevention of Early Asthma in Kids (PEAK) Trial. The cohort is population based and identified by primary care physicians within the cities of the 5 clinical centers (listed in the Appendix in the Journal's Online Repository at www.mosby.com/jaci) on the basis of identification of children with recurrent wheeze. Children were then screened for eligibility for enrollment on the basis of the study inclusion and exclusion criteria that have been published in more detail elsewhere.[4]

The original Asthma Predictive Index (API) was based on data from the Tucson Children's Respiratory Study (TCRS), a large and

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TABLE I. mAPI* versus original API (Castro-Rodriguez et al[3])

1. The child must have a history of 4 or more wheezing episodes with at least one physician diagnosis.
2. In addition, the child must have a history of 4 or more wheezing episodes with at least 1 confirmed by a physician.

mAPI: Major criteria	**Original API: Major criteria**
• Parental history of asthma	• Parental history of asthma
• Physician-diagnosed atopic dermatitis	• Physician-diagnosed atopic dermatitis
• **Allergic sensitization to ≥1 aeroallergen**	
mAPI: Minor criteria	**Original API: Minor criteria**
• **Allergic sensitization to milk, egg, or peanuts**	• **Physician-diagnosed allergic rhinitis**
• Wheezing unrelated to colds	• Wheezing unrelated to colds
• Blood eosinophils ≥4%	• Blood eosinophils ≥4%

*Differences in indices are in bold.

Abbreviations used

API: Asthma Predictive Index
CAMP: Childhood Asthma Management Program
CARE: Childhood Asthma Research and Education Network
mAPI: Modified Asthma Predictive Index
NHLBI: National Heart, Lung, and Blood Institute
OR: Odds ratio
PEAK: Prevention of Early Asthma in Kids
SPT: Skin prick test
TCRS: Tucson Children's Respiratory Study

longitudinal assessment of respiratory illnesses in more than 1200 children.[5,6] The API included frequent wheezing in the first 3 years of life and either one major risk factor (parental history of asthma or personal history of atopic dermatitis) or 2 of 3 minor risk factors (eosinophilia, wheezing without colds, and allergic rhinitis; Table I).[3] The API had a positive predictive value for active asthma of 47.5% to 51.5% between the ages of 6 and 13 years. Conversely, only 5% of children with a negative API result had active asthma between the ages of 6 and 13 years. Therefore children with a positive API result are likely to go on to have persistent asthma. The PEAK trial modified the published API to include 2-year-old children because PEAK is an asthma prevention study directed at early intervention in high-risk children.[4] The 2-year-old children in PEAK possessed similar API characteristics as the 3-year-old children, including wheezing burden and sensitization. Although it was not evaluated during the Tucson study, allergic sensitization to aeroallergens and allergic sensitization to milk, eggs, or peanuts during the first years of life have been reported as risk factors for the subsequent development of persistent asthma in the literature.[7-12] Because allergic rhinitis can be difficult to diagnose in young children, the published API was also modified (Table I) for use in the PEAK study to include allergic sensitization to aeroallergens and to foods and was used in its place with the expectation of at least a similar positive predictive value for asthma. Because food sensitization[10,11] and not definitive food intolerance caused by allergy has been used for asthma prediction, food challenges to confirm food allergy in those participants with food sensitization were not performed as part of PEAK.

To focus on the API major criteria revealed in the TCRS cohort[3] in this analysis, we examined the atopic profile of a subset of toddler-aged children enrolled in the PEAK study with frequent wheeze at high risk for the development of asthma who either had a parental history of asthma, a personal history of atopic dermatitis, or both.

Study design

PEAK is a multicenter, double-blind, randomized, placebo-controlled, parallel-group comparison of inhaled fluticasone propionate with placebo in children. It is a long-term trial developed by the National Heart, Lung, and Blood Institute (NHLBI)–sponsored Childhood Asthma Research and Education (CARE) Network (see the Appendix in the Journal's Online Repository). During the enrollment and randomization study visits, data were collected on family and personal medical history, environmental history, medication use, and quality of life on the basis of questionnaire results, physical examination findings, lung function testing, eosinophil counts, IgE, and allergy skin prick tests (SPTs). A detailed description of the screening, recruitment, design, and statistical analysis for the PEAK study is reported elsewhere.[4] The primary outcome of this ongoing study is to assess whether chronic and early therapy with inhaled corticosteroids initiated in children 2 and 3 years of age at high risk of asthma can prevent the development of persistent asthma at 4 to 6 years of age. It is currently being conducted in accordance with the principles of the Declaration of Helsinki and has been approved by the NHLBI, the CARE Network Steering Committee, the CARE Network Protocol Review Committee, the CARE Network Data Safety Monitoring Board, and the local institutional review boards at all participating centers. Parents provided informed consent.

Procedures

All of the PEAK participants (n = 285) were evaluated for the presence of allergic sensitization by means of SPT or specific IgE assessment (Pharmacia CAP system [CAP FEIA]; Pharmacia, Uppsala, Sweden) techniques.[4] If a child was suspected to have had an anaphylactic reaction to any tested allergen, a CAP FEIA test was performed instead of skin testing; a level of 0.35 IU/mL or greater was considered positive, as specified by the manufacturer and other studies.[13] Two hundred fifty-seven children were evaluated by means of skin testing alone, 15 by means of CAP FEIA alone, and 13 by means of both methods.

The atopic profile was further characterized with peripheral blood eosinophil percentages by means of automated assay at each center in 198 children. An eosinophil count of 4% or greater was considered increased. This is greater than the 90th percentile of the normal value in a birth cohort of 900 nine-month-old infants (unpublished data from the Tucson Children's Respiratory Study). Total serum IgE (Pharmacia CAP system) levels were measured at each clinical center on serum from blood clotted at room temperature for 226 children. SPTs were performed by PEAK-certified personnel in accordance with a study-specific protocol on the basis of that used in the Childhood Asthma Management Program (CAMP) study and the National Cooperative Inner-City Asthma Study.[14,15] Allergy skin

TABLE II. Demographics and asthma characteristics of the PEAK cohort

Characteristic	Mean ± SD or n (%), n = 244
Age, mo	35.9 ± 7.0
Race or ethnic group no. (%)	
Non-Hispanic white	130 (53.3)
Non-Hispanic black	29 (11.9)
Hispanic	53 (21.7)
Other	32 (13.1)
Sex, no. (%)	
Female	96 (39.3)
Male	148 (60.7)
Parental history of asthma, no. (%)	
Maternal history	111 (45.5)
Paternal history	91 (37.3)
Both	20 (8.2)
Parental history of atopy, no. (%)	
Maternal history	105 (43.0)
Paternal history	83 (34.0)
Both	44 (18.0)
Cigarette exposure first 2 years of life, no. (%)	
Maternal smoking	37 (15.2)
Paternal smoking	53 (21.7)
Other household member smoking	43 (17.6)
Age of first asthma diagnosis by a physician, mo	16.0 ± 9.9
Children with pets in house, no. (%)	143 (58.6)
Hospitalizations for asthma in year before enrollment, no./100 person-years	6.7 ± 0.64
Recordings during enrollment month (average days per week)	
Albuterol use	1.0 ± 1.2
Night awakenings	0.5 ± 0.7

tests were performed to 8 common aeroallergens at all the clinical centers (mixtures for house dust mite [*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*], cockroach [American and German], dog [mixed breeds], cat [standardized], mold [mix no. 1], grass [standardized Southern mix], tree [eastern 8 tree mix], and weed [national mix] and 3 foods [cow's milk, chicken and whole egg, and peanut; Greer Laboratories, Lenoir, NC) by using the Multi-test II (Lincoln Diagnostics, Decatur, Ill) prick technique. The St Louis center tested the following additional allergens: red oak, *Aspergillus fumigatus*, and short ragweed (Greer Laboratories). A test response was considered positive if the prick test resulted in a wheal with a mean diameter (mean of maximum and 90° midpoint diameters) that was at least 3 mm greater than that produced by a saline control.[4] Questionnaire data were collected at the time of enrollment from the child's parents regarding baseline medical, demographic, and atopic history.

Data analysis

Double data entry was used, with both the clinical center entering the data in real time by using a Web-based database and second entry from data at the data-coordinating center to ensure accuracy. Discrepant values were resolved by the clinical centers. All analyses were carried out with version 8.2 of the SAS statistical software system (SAS Institute Inc, Cary, NC). Descriptive statistics, including mean, median, SD for continuous variables, and frequency tables for discrete variables, were generated. Associations between demographic factors and allergic sensitization were characterized by using contingency table analysis. Significance levels were determined by using the Pearson χ^2 statistic and confirmed by using the Fisher exact test in the case of sparsely populated tables. Multivariable logistic regression was used to assess associations between allergic sensitization and predictor variables, including atopic dermatitis, eosinophil percentages, serum total IgE levels, clinical center, age, sex, race, and parental history of asthma. Both P values corresponding to the contingency table analysis (unadjusted P value) and the multivariable analysis (adjusted P value) were reported in any instance in which they differed. The total serum IgE level was converted to an ordinal scale and classified according to the quartiles of the total serum IgE levels on the continuous scale. Associations between eosinophil percentages and IgE and demographic factors were characterized by means of ANOVA, and significance levels were determined by using the F statistic and confirmed with nonparametric Kruskal-Wallis tests in the case of maldistribution. Two-sided P values of less than .05 were considered statistically significant.

RESULTS

PEAK cohort demographics

Complete data were available for 244 participants with either a parental history of asthma, a personal history of atopic dermatitis, or both randomized to the PEAK study (Table II). Participants were children with a mean ± SD age of 36 ± 7 months who were predominately male (60.7%) and non-Hispanic white (53.3%), with an age of physician diagnosis of asthma of 16.0 ± 9.9 months in 86% of participants who had received this diagnosis and experienced 6.7 ± 0.64 hospitalizations for wheezing per 100 person-years (Table II). All participants had at least 4 episodes of wheezing lasting at least 24 hours in the 12 months before enrollment. The participants experienced a mean and standard deviation per week of 1.0 ± 1.2 days of albuterol use and 0.5 ± 0.7 night awakenings as recorded on daily diary cards during the month of study run-in, during which they received no medications except albuterol as needed. No significant associations ($P > .05$) were appreciated for food and aeroallergen sensitization and the number of hospitalizations, use of albuterol, or number of nocturnal awakenings recorded during the enrollment month.

Modified API characteristics

Of the 244 participants, 90.3% met the mAPI criteria on the basis of a history of either a positive parental history or personal history of atopic dermatitis. All 3 major mAPI criteria (parental history of asthma, personal history of atopic dermatitis, and ≥1 positive aeroallergen skin test response) were satisfied by 19% of the cohort. Two hundred forty-four subjects were either tested for allergen sensitization by means of SPT (91.7%) or CAP FEIA (8.3%). Of these, 60.7% (n = 148) demonstrated allergen sensitization. Of this cohort, 6.6% (n = 16) had food sensitization alone, 28.3% (n = 69) had aeroallergen

sensitization alone, and 25.8% (n = 63) had sensitization to both (Fig 1; Table E1 in the Journal's Online Repository at www.mosby.com/jaci).

Male children were significantly more likely to be sensitized to any allergen (66.2%, n = 98, adjusted $P = .03$) and sensitized to an aeroallergen specifically (59.5%, n = 88, adjusted $P = .04$). Younger children 24 to 36 months of age had a similar rate of allergic sensitization to children older than 36 months of age.

Sensitization to any allergen was higher in the group that had a personal history of atopic dermatitis with or without parental history of asthma compared with in the group that had a parental history of asthma alone (66.1% vs 51%, $P = .04$). In children who met the mAPI criteria on the basis of a parental history of asthma alone, sensitization to any allergen was higher in the older compared with the younger participants (63.8% and 40.0%, respectively; $P = .02$). Children given a physician diagnosis of allergic rhinitis (20.3%, n = 30) were more likely to be sensitized to either a food allergen or aeroallergen ($P = .012$). Children with history of at least daily asthma-like symptoms, such as cough, wheeze, shortness of breath, and chest tightness (8.1%, n = 12), were not more likely to be sensitized to any allergen than children with less-frequent symptoms ($P = .32$).

Children who had a pet in their home were more likely to be sensitized to any aeroallergen than those who did not live with a pet ($P = .015$, Table E2 in the Journal's Online Repository at www.mosby.com/jaci). However, children who lived with pets were just as likely to be allergic to cats and dogs as those children who did not (58% [n = 87] vs 59.3% [n = 54], respectively; $P = .84$). Children who had environmental tobacco smoke exposure in the first 2 years of life were not more likely to be sensitized than children who did not have such exposure (Table E2 in the Journal's Online Repository). Parental history of asthma was not a significant predictor of sensitization (odds ratio [OR], 1.6; 95% CI, 0.35-7.23) in multivariate logistic regression. Those children who had a maternal history of asthma were not more likely to be sensitized to an aeroallergen or food allergen than those with a paternal history (30% [n = 33] vs 25% [n = 27], respectively; $P = .39$).

Children had a mean eosinophil percentage of 4.1% ± 3.04% (range, 0% to 23%). Male participants were also more likely to have an eosinophil percentage of 4% or greater compared with female participants (48.3% vs 35.1%, respectively; adjusted $P = .05$; Table E1 in the Journal's Online Repository). Children 36 months or older were more likely to have increased eosinophil counts when compared with those younger than 36 months of age (48.7% vs 37.5%, respectively; $P < .05$). An eosinophil percentage of 4% or greater (OR, 2.3; 95% CI, 1.1-4.5) and a total serum IgE level of greater than 100 IU (<10 IU vs >100 IU [OR, 5.7; 95% CI, 2.1-15.9], 10-40 IU vs >100 IU [OR, 3.5; 95% CI, 1.3-9.9], and 41-100 IU vs >100 IU [OR, 2.8; 95% CI, 1.1-7.5]) were the only significant predictors of aeroallergen sensitization among demographic, parental history, and atopic risk factors in a multivariate logistic regression. However, a total serum IgE level of greater than 100 IU (<10 IU vs >100 IU [OR, 4.5; 95% CI, 1.6-12.5], 10-40 IU vs >100 IU [OR, 3.5; 95% CI, 1.4-8.8], and not eosinophil percentage [OR, 1.1; 95% CI, 0.5-2.2]) was a significant predictor of food allergen sensitization.

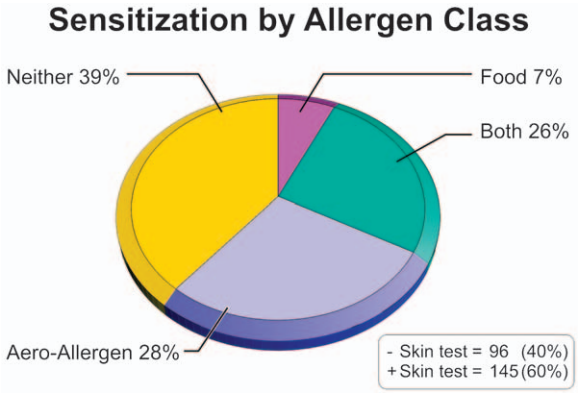

FIG 1. Distribution of allergic sensitization by SPT or CAP FEIA in the PEAK cohort.

Male participants (81.4%, n = 48) were more likely than female participant to have a total IgE level of 100 IU or more ($P = .0004$). No significant differences in total IgE levels were found between age groups on the basis of history of physician-diagnosed allergic rhinitis.

Those children with a family-reported ethnic background of African American were more likely to be sensitized to either at least one food allergen (55.2%, n = 16; $P = .01$; adjusted $P = .10$) or aeroallergen (79.3%, n = 23; unadjusted $P = .01$; adjusted $P = .05$) than participants who reported other ethnic origins. No differences were seen in peripheral eosinophil percentages or total IgE levels between subjects with varying family-reported ethnic backgrounds ($P = .13$). The difference between the unadjusted and adjusted P values corresponding to the association between ethnicity and allergic sensitization is due to a confounding between ethnicity and clinical center. In particular, one clinical center had a significantly lower rate of participant sensitization and also had a lower percentage of minority ethnic participation. Because the apparent ethnic differences in sensitization might actually be due to geographic differences in sensitization, these results must be considered to be inconclusive.

DISCUSSION

PEAK is the first clinical trial to enroll participants on the basis of a high-risk index known as the API.[3] Children with a positive API have been shown to be likely to go on to have persistent asthma.[3] PEAK therefore has the potential to examine the atopic and asthmatic characteristics of a high-risk cohort with frequent intermittent wheezing episodes who are likely to have persistent asthma.

In this analysis we examined a young group of children with frequent wheezing and at least one of the 2 major criteria of the API.[3] This study finds that toddlers

at high risk of development of persistent asthma are frequently sensitized in early life to allergens, particularly aeroallergens. Two thirds of this high-risk cohort of 2- and 3-year-old children were sensitized to either aeroallergens, food allergens, or both. This degree of allergic sensitization is higher than the 23% to 50% prevalence reported in cohorts of similarly aged wheezing children selected on the basis of a history of only personal intermittent wheezing[16-18] or only a parental history of atopy (unpublished data from R. F. Lemanske).[10,20,21] It is, however, more comparable with the degree of sensitization observed in cohorts of young children with frequent wheezing responsive to asthma medication (51% to 58%).[6,19]

There appears to be early activation of the immune system involved with allergic inflammation, with demonstrable IgE antibody formation to both food allergens and aeroallergens. The high frequency of aeroallergen sensitization suggests that aeroallergens might have an important role in the early developmental stages of asthma. Children who had a personal history of atopic dermatitis had higher sensitization rates compared with those who had only a parental history of asthma. Allergic sensitization to foods alone was uncommon (7% of the cohort), and the prevalence of sensitization did not differ between the 2- and 3-year-old age groups. Thus sensitization to aeroallergens appears to begin early in life in these high-risk children, a process that might initiate or perpetuate allergic inflammatory responses within the airways and contribute to asthma pathogenesis and the so-called allergic march. This has implications for the management of these high-risk children and the potential prevention of persistent asthma through early intervention with asthma medications or environmental control.

Similar to previous reports, male children and those with a family-reported African American background demonstrated increased allergen sensitization, reaching nearly 80% by 4 years in the latter.[20,21] Increasing rates of hospitalizations and mortality have been described in African American asthmatic patients,[22,23] which potentially could be a result of increased allergic sensitization and chronic exposure to those allergens. However, significant differences in sensitization were seen between clinical centers, with a range of between 45% and 82%. This might be due in part to the ethnic differences between the populations of both cities, with St Louis having a greater percentage of persons reported as having African American background and also performing a greater number of skin tests. This confounding variable, clinical center, does not allow us to definitively characterize differences in sensitization across ethnic groups. Another explanation might be the differences in aeroallergen composition between these 2 cities, with Denver reporting a lower rate of dust mite sensitization.[24] However, it should be noted that similar rates of sensitization to different allergens have been reported in environments with varying rates of dust mite sensitization.[25-28]

Personal atopic dermatitis is more predictive of sensitization in younger children than a parental history of asthma. Unlike a previous report,[6] a maternal history of asthma did not confer a higher risk of sensitization in the PEAK cohort that might be overshadowed by selection of a high-risk cohort identified by an API. This suggests that atopic dermatitis is a more powerful surrogate for sensitization than parental history because it is evidence of established personal atopy. Parental history of asthma appears to be a more important factor in the older child without established personal atopic dermatitis. In fact, maternal history is important in univariate analysis as a risk factor for asthma, but once allergic rhinitis and atopy covariates are added to a multivariate model for asthma, parental history becomes nonsignificant (unpublished data from the TCRS).

Children who lived with pets were more likely to be sensitized to any aeroallergen than those who did not live with a pet. The protective effect of living with a pet early in life was not seen in these 2- and 3-year-old children. However, previous reports suggest that the exposure might be protective if it occurs within the first year of life[29-31] and might be detrimental if it occurs after the child is sensitized.[32-34] We did not obtain data if the pet was present in the home at birth and therefore cannot address this issue. The PEAK study also selected a group of children at high risk for the development of atopy and for which exposure to pets might not have a significant protective effect. An additional finding was that those children living with a cat or dog were not more likely to be sensitized to pet dander than those who did not. Recent reports have indicated that pet ownership is not necessarily required for sensitization to pet dander[35,36] because exposure to allergen found in schools and other nondomiciliary settings[37] might be sufficient to lead to sensitization. In addition, children in the PEAK study who were exposed to parental cigarette smoke in the first 2 years of life were not more likely to be sensitized than children who were not. This is not supportive of previous findings that found that children exposed to cigarette smoke in early life are more likely to become atopic.[34-39] However, PEAK does not possess the power of a large and longitudinal study to detect such a difference.

Eosinophils and IgE levels, biomarkers of atopy, were significantly increased in male participants. No ethnic differences were observed in blood eosinophil counts or IgE levels, but as noted earlier, the data on ethnicity is limited by confounding by clinical center.

Many similarities can be drawn between the cohorts in the PEAK and CAMP trials. CAMP was a study of more than 1000 older children, 5 to 12 years of age, with documented persistent asthma.[38] Both the PEAK and CAMP cohorts evidenced a male predominance, a high degree of allergen sensitization and eosinophilia, a strong family history of asthma and atopy, and a majority of home environments with cats and dogs.[22,39] The cohorts differed in asthma severity, with PEAK and CAMP consisting, respectively, of intermittent wheezers and mild-to-moderate persistent asthmatic children. It is reasonable to speculate that the PEAK cohort represents a cohort similar to the CAMP cohort but before persistent asthma has

developed. As such, the PEAK cohort appears to be an appropriate group to attempt secondary asthma prevention with inhaled corticosteroids.

Acknowledgement of the personnel of the CARE Network has been provided in the Appendix, which can be viewed in the Journal's Online Repository at www.mosby.com/jaci.

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The Asthma Predictive Index: A very useful tool for predicting asthma in young children

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Recurrent wheezing is a common problem in young children: approximately 40% of children wheeze in their first year of life. However, only 30% of preschoolers with recurrent wheezing still have asthma at the age of 6 years. Nevertheless, asthma, the most prevalent chronic disease in children, is difficult to diagnose in infants and preschoolers. This article reviews the importance of determining at an early age which infants/preschoolers will have asthma later in life, analyzes the pros and cons of different predictive indices, and discusses the efficacy of the Asthma Predictive Index. (J Allergy Clin Immunol 2010;126:212-6.)

Key words: *Infants, preschoolers, wheezing, asthma, clinical score, asthma predictive index*

Which infants/preschoolers with recurrent wheezing will have asthma at school age? This is an important question; asthma, the most prevalent chronic disease in children, is one of the most difficult disorders for physicians to diagnose in infants/preschoolers. Approximately 40% of all young children worldwide have at least 1 episode of asthmatic symptoms, such as wheezing, coughing, or dyspnea.[1,2] Moreover, approximately 80% of the asthmatic subjects have the disease in the first years of life.[3] However, only 30% of preschoolers with recurrent wheezing still have asthma at the age of 6 years.[4] Recent data from the National Center for Health Statistics[5] showed that even though asthma prevalence was lower among preschool-aged children compared with school-aged children and adolescents, ambulatory care visits, emergency department visits, and hospital discharges were considerably greater for infants/preschoolers (0-4 years). A Swiss study[6] showed that children less than 3 years of age had significantly worse asthma control (more sleep disturbance, limitations in play and family activities, emergency department or general practitioner visits, and hospitalizations) compared with school-children and adolescents. This article reviews the importance of determining at early ages which infants/preschoolers will have asthma later in life and proposes the use of the Asthma Predictive Index (API) to identify these children.

Abbreviation/Acronyms used

API: Asthma Predictive Index
FeNO: Fraction of exhaled nitric oxide
mAPI: Modified Asthma Predictive Index
PIAMA: Prevention and Incidence of Asthma and Mite Allergy
RCT: Randomized clinical trial

BACKGROUND

Unfortunately, infants who wheeze and eventually have asthma coexist with a large group of infants with recurrent wheezing whose symptoms are transient and usually subside during early years of school. It is a challenge to distinguish between these groups during infancy and early childhood simply on the basis of clinical presentation. No accurate screening tests (using genetic or single biochemical markers) have been developed to determine which young children with recurrent wheezing will have asthma.[7] Chronic inflammation is the most common feature of asthma, but measurements of inflammation are not yet a major factor in diagnosing and monitoring asthma. The best measurements of airway inflammation are made by using bronchoscopy with analysis of biopsy specimens, bronchoalveolar lavage samples, or both, procedures that are too invasive for routine use in children. Other noninvasive techniques (eg, measuring biomarkers of inflammation in exhaled breath condensate) are being tested in longitudinal studies for their efficacy in early diagnosis of asthma.[8] Therefore the diagnosis and management of asthma in young children are primarily based on subjective clinical features and findings from medical examinations.

A study of 95 children in Australia found that airway responsiveness at 1 month of age is a good predictor of airway function and lower respiratory tract symptoms at the age of 6 years.[9] However, a study of 129 children in France showed, after multivariate analysis, that early bronchial hyperresponsiveness in infants who wheezed did not predict the persistence of asthma between 5 and 9 years of age; in contrast, family history of atopy was the only significant risk factor.[10] Other studies showed that wheezing in the first 3 years of life was a poor predictor of subsequent asthma; instead, atopy in early life predicted future airway disease.[11,12] Matricardi et al[13] investigated the outcomes of wheezing using the Multicentre Allergy Study, a birth cohort study of 1,314 infants selected based on increased levels of IgE in cord blood, at least 2 atopic family members, or both.[13] They associated wheezing at the age of 13 years with atopy in parents and IgE sensitization to common allergens, increased total IgE levels, and exposure to high levels of indoor allergens in the first 3 years of life. A different study reported that serum levels of soluble IL-2 receptor (a sophisticated biomarker) predicted persistent wheezing for at least 12 months among atopic infants.[14] On the contrary, the

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Major Criteria	Minor Criteria
1. Parental MD asthma †	1. MD allergic rhinitis §
2. MD eczema ‡	2. Wheezing apart from colds
	3. Eosinophilia (≥4%)

*Loose index for the prediction of asthma: early wheezer plus at least one of two major criteria or two of three minor criteria. Stringent index for the prediction of asthma: early frequent wheezer plus at least one of the two major criteria or two of three minor criteria.

†History of a physician diagnosis of asthma. ‡Physician diagnosis of atopic dermatitis at age 2 or 3. §Physician diagnosis of allergic rhinitis at age 2 or 3.

FIG 1. Asthma Predictive Index.*[15]

risk for transient wheezing during the first 3 years of life among children who did not wheeze by school age included low baseline levels of lung function, maternal smoking during pregnancy, and lower maternal age.[4]

API AND OTHER INDICES

The API was developed 10 years ago by using data from 1246 children in the Tucson Children's Respiratory Study birth cohort. It was based on factors that were found during the first 3 years of life to predict continued wheezing at school age.[15] A positive API score requires recurrent episodes of wheezing during the first 3 years of life and 1 of 2 major criteria (physician-diagnosed eczema or parental asthma) or 2 of 3 minor criteria (physician-diagnosis allergic rhinitis, wheezing without colds, or peripheral eosinophilia ≥4%). A loose index (<3 episodes/y and 1 of the major or 2 of the minor criteria) and a stringent index (≥3 episodes/y and 1 of the major or 2 of the minor criteria) were created (Fig 1).[15] A positive stringent API score by the age of 3 years was associated with a 77% chance of active asthma from ages 6 to 13 years; children with a negative API score at the age of 3 years had less than a 3% chance of having active asthma during their school years.

After the API was created, other scores were developed to predict which preschoolers with recurrent wheezing would have asthma at school age. In 2003, Kurukulaaratchy et al[16] used data from 1456 children in the Isle of Wight birth cohort to devise a scoring system based on 4 factors: family history of asthma, recurrent chest infections in the second year of life, atopic sensitization at 4 years of age, and absence of recurrent nasal symptoms in the first year of life. These factors confer a high risk for wheezing persistence at 10 years of age.

In 2008, Devulapalli et al[17] performed a nested case-control study of 449 children in Norway and created a simple scoring system based on obstructive airway disease scores: scores of 5 or greater (range, 1-12) by 2 years of age are a risk factor for asthma at 10 years of age. In 2009, Caudri et al[18] developed a clinical scoring system using data from 3963 children from the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort in The Netherlands, in which participants were assessed on a yearly basis until the age of 8 years. Using data from a subgroup of children with reported wheezing or coughing at night (without a cold) until 4 years of age, they assessed possible predictors for asthma at 7 to 8 years of age. They found that male sex, postterm delivery, parental education, inhaled medication, wheezing frequency, wheezing/dyspnea apart from colds, respiratory tract infections, and eczema all independently predicted asthma. The authors established a risk score based on these 8 clinical parameters (cutoff of ≥20 as a positive value).

These 3 asthma indices are based on diverse variables,[15,16,18] and that condition could make a difference as to which index would have more success in different populations worldwide. The API has 5 parameters, whereas the Isle of Wight and PIAMA indices have 4 and 8 parameters, respectively (Table I).[15,16,18] Two studies included some reference to a family history of asthma.[15,16] Only 2 studies mention eczema,[15,18] nasal symptoms,[15,16] wheezing apart from colds,[15,18] or respiratory tract/chest infections.[16,18]

Children who experience early onset of allergic sensitization and respiratory tract illnesses that include wheezing are believed to be at the highest risk for persistent asthma. However, it is possible that recurrent chest infections identified in the Isle of Wight study or respiratory tract infections reported by the PIAMA cohort were actually misreported episodes of recurrent wheezing[19]; the definition of respiratory tract/chest infection might vary among populations. Because the relationship between virus-induced wheezing and asthma depends on the virus (eg, infants who wheeze from infection with rhinoviruses have a high risk for subsequent asthma) and because information about virus types was not reported for the Isle of Wight and PIAMA cohorts, further research is needed to identify viral factors that lead to asthma. In addition, the use of inhaled medication and level of parental education[18] depend on local public health strategies and social opportunities, respectively. Sex was included as a risk factor in 1 index.[18] The prevalence of asthma among each sex varies with age; in the first years of life, asthma is more prevalent in boys, but in adolescents it predominates among female subjects. Moreover, there are sex differences in the experience of asthma-like symptoms, the diagnosis of asthma, and the use of asthma medications.[20]

Several years ago, it was reported that allergic sensitization to aeroallergens and foods in early life was associated with asthma at school age.[21,22] More recently, a study from Germany found that asthma among subjects who were 7 to 22 years of age was associated with allergic sensitization by a specific IgE during the first 2 years of life but only if a positive parental history of asthma was present.[23] Among biomarkers used in the asthma predictors described above, eosinophilia is a minor criterion for asthma diagnosis in the API,[15] and allergic sensitization, based on skin prick test response, is a criterion of the Isle of Wight index.[16] A modified API (mAPI),[24] which was tested in a randomized trial of 285 subjects, incorporated allergic sensitization to 1 or more aeroallergens as a major criterion and allergic sensitization to milk, eggs, or peanuts as a minor criterion, replacing physician-diagnosed allergic rhinitis from the original API. However, the API, rather than the mAPI, is used to predict asthma in longitudinal studies.[25,26] In most health care settings, it is easier, cheaper, and probably more reliable (allergens vary with region) to determine eosinophilia counts in blood samples than to determine allergic sensitization with a skin prick test or by measuring specific IgEs. The members of the Multicentre Allergy Study performed multiple skin and IgE tests on subjects throughout childhood and used mathematic modeling to show that specific IgE responses did not reflect a single phenotype of atopy; only atopy to multiple factors at early ages predicted asthma at the age of 8 years.[27]

The ability of a segmentation mathematic model of analysis to predict asthma was tested in France with infants less than 30 months of age who had recurrent wheezing. It showed that a lack

TABLE I. Characteristics of the API[15] and Isle of Wight[16] and PIAMA[18] indices

	API	Isle of Wight	PIAMA
Year of publication	2000	2003	2009
Country	United States	United Kingdom	The Netherlands
No. of children in birth cohort	1246	1456	3963
Age of asthma prediction (y)	6-13	10	7-8
No. of parameters used	5	4	8
Parameters			
Family history of asthma	✓	✓	✓
Eczema	✓		✓
Nasal symptoms	✓	✓	
Wheezing without colds	✓		✓
Peripheral eosinophilia	✓		
Atopic sensitization (skin prick test)		✓	
Respiratory tract/chest infections		✓	✓
Sex			✓
Inhaled medication use			✓
Parental education			✓
Postterm delivery			✓

TABLE II. Values from the API[15] and Isle of Wight[16] and PIAMA[18] indices

Risk of asthma	Sensitivity	Specificity	Positive predictive value	Negative predictive value	+ LR	− LR
API*						
At 6-8 y	22	97	77	90	7.3	0.80
At 11-13 y	15	97	47	85	5	0.88
At 6-13 y	16	97	77	68	6.0	0.86
Isle of Wight† at 10-11 y	10	98	83	64	7.9	0.91
PIAMA‡ at 7-8 y	60	76	23	94	2.5	0.53

+ LR, Positive likelihood ratio (sensitivity/1-specificity); *− LR*, negative likelihood ratio (1-sensitivity/specificity).
*Positive stringent index.
†Risk score strata = 4.
‡Cutoff ≥20.

of eosinophilia in wheezing infants without ongoing infections was a better predictor of remission of wheezing by the age of 6 years than measurements of allergic sensitization or total serum levels of IgE.[28] An absence of eosinophilia alone predicted 91% of remissions of wheezing in infants; when combined with an absence of allergic sensitization, remission was correctly predicted in 96.9% of the cases. A subsequent analysis from the Tucson Children's Respiratory Study associated persistent eosinophilia throughout childhood (until the age of 11 years) with the presence of chronic asthma independently of atopy.[29] It should be noted that detection of eosinophilia in blood samples also predicts persistent asthma in infants with severe lower respiratory tract infections, such as bronchiolitis and pneumonia.[30,31]

There are other important differences among the asthma predictive indices: the API uses a major and minor criteria system based on a univariate analysis of the cohort, whereas the PIAMA index uses a more complicated approach, with odds ratios for individual predictors determined from multivariate analyses. The PIAMA system thereby generates a more accurate predictive model, but the score is somewhat laborious to determine because the different factors have different weights. Scores will be calculated and used by busy clinicians only if they are easy to remember and use or if they come packaged with a clinical information system, have been validated in different populations, and improve patient outcome. Moreover, clinicians are wary of predictive indices that have not been validated in different settings, particularly in their own. The API was developed by using a mixed-ethnicity, unselected birth cohort. In contrast, no ethnic mix was included in the Isle of Wight cohort, and the PIAMA cohort was selected based on allergic screening results. The sensitivity, specificity, and positive and negative predicted values for development of asthma among different age groups are compared between the stringent API, PIAMA index, and Isle of Wight index in Table II.[15,16,18]

Sensitivity and specificity provide a perspective of the population that often exaggerates the diagnosis and certainty of the test from the level of individual patients. This is overcome by the use of positive and negative predictive values, but these are influenced by the prevalence of asthma in the population studied. The stringent API has the best combination of sensitivity (although it is low), specificity, and predictive value of the indices compared (Table II). Another way to set cutoff points for diagnostic tests is through analysis of receiver operating characteristic curves. Only the PIAMA index includes this type of analysis in determination of the predictive score; determination of API scores does not require it. Another approach to analyze the results (categorical or continuous) of a diagnostic test is to determine the likelihood ratio, which is relevant clinical practice. The positive and negative likelihood ratios of API, PIAMA index, and the Isle of Wight index scores are also presented in Table II; the LR for positive results from the API and the Isle of Wight indices are similar and good enough to apply in the general population, and useful to certify diagnosis of asthma. This is justified by the fact that pretest could change from 30% to more than 80%.

APPLICATIONS

Among the 3 asthma predictive indices discussed, the API is the only one tested in different populations and in independent studies, such as randomized clinical trials (RCTs).[32,33] The API is also the only index used in studies to determine relationships between biomarkers, such as comparing fraction of exhaled nitric oxide (FeNO)[25,34] or early lung function (Garcia-Marcos, personal communication). Recently, a prospective cohort study of 391 young children (age, 3-47 months) showed that wheezy young children with a stringent API have increased levels of FeNO compared with those seen in children with recurrent wheeze and a loose API or children with recurrent cough.[25]

Because asthma is one of the most prevalent chronic diseases, most potentially asthmatic children are identified in primary health settings, where sophisticated, noninvasive biomarkers (eg, exhaled breath condensate and FeNO) and tests, such as dynamic spirometry and airway resistance measurements, are difficult and expensive to implement. The stringent API is a simpler and less expensive tool to identify children at risk for asthma. A study showed a higher variance in prescribing patterns among general practitioners for asthmatic children less than 6 years old than for older children; this might result from the complexities of diagnosing asthma in young children. Parental asthma was the only family variable that correlated with prescription of asthma medication, even after adjustment for asthma diagnoses.[35] Doctors instinctively use multiple parameters to make management decisions based on their own training and personal experience. Therefore before they begin using a predictive index, they need to be convinced that it will improve the care of their patients.

The original goal of the API was to identify subgroups of preschoolers with recurrent wheezing who were at greatest risk for asthma later in life. However, the major asthma guidelines, such as the international Global Initiative for Asthma[36] and the American guidelines,[37] now recommend using the API in deciding whether to initiate controller therapy in children who wheeze at ages of 0 to 4 years. Health care providers are encouraged to begin controller therapy if a child has experienced at least 4 episodes of wheezing in the past year and has a positive API score or if a child has at least 2 exacerbations that require treatment with systemic corticosteroids in a 6-month period. These recommendations will likely decrease morbidity in the preschool-aged group but will not modify the natural course of asthma; this was demonstrated in a study of children aged 2 to 3 years with positive mAPI scores who were treated with fluticasone for 2 consecutive years.[33] Not all children who wheeze have asthma, and the term asthma, without any qualification or definition, has begun to hinder rather than facilitate progress in the management of wheezy children.[38] This is particularly relevant to children in the preschool years, when wheezing syndromes are especially common and no objective reliable test exists to assist physicians in diagnosing asthma and establishing appropriate therapy. A recent RCT[33] of 238 children 12 to 59 months old with moderate-to-severe intermittent wheezing and a positive mAPI score showed benefits from short-term therapy with wet nebulized budesonide or oral montelukast. However, for children with a negative mAPI score, neither treatment led to significant improvements in wheezing compared with use of a β-agonist alone. The absence of a detectable effect in this group might be the result, in part, of smaller sample and effect sizes and thus lower power. Therefore more RCTs need to be performed with children with positive and negative API scores to compare the effects of different therapies.

CONCLUSIONS

The most impressive aspect of the API is its ability to rule out the likelihood of asthma by school age in young children with wheezing.[39] For children who are "early wheezers during the first 3 years of life," API negative predictive values ranged from 93.9% at 6 years of age to 86.5% at 13 years of age. For children who are "early frequent wheezers during the first 3 years of life," the negative predictive values were 91.6% and 84.2% for 6 and 13 years of age, respectively. Considering the multiple causes of wheezing among preschoolers and the heterogeneity of childhood asthma, it might be impossible to develop a more accurate predictive model without increasing the number of variables. Factors such as genetic polymorphisms, environmental and socioeconomic factors, sex, ethnicity, and family health beliefs might also be taken into account.[19] Even if an index is accurate, it must be easy to apply, validated in different populations, and shown to improve patient outcome to be used by busy clinicians. The simplicity of the API allows its use in every health care setting worldwide.

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